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Germline Pathogenic Variants Among Participants with Neuroendocrine Tumors in the Healthy Nevada Project

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BACKGROUND

The genetic drivers of neuroendocrine tumors (NET) remain incompletely defined, with emerging evidence suggesting potential links to hereditary cancer syndromes. The Healthy Nevada Project (HNP), a large, population based genomic screening initiative offers a unique opportunity to explore the prevalence of pathogenic germline variants associated with NETs.

METHODS

We evaluated germline genomic data from 98 participants enrolled in the HNP with a diagnosis of NET on a set of internal clinical sources that includes, but is not limited to, the problem list and medical history. Pathogenic or likely pathogenic variants were identified based on curated evidence in a panel of 74 genes previously associated with cancer risk, hereditary cancer syndromes, or of potential relevance to NET biology.

RESULTS

Of the 98 individuals with a diagnosis of a NET, 15 (15%) carried pathogenic or likely pathogenic germline variants according to ClinVar or VEP annotations for novel variants. The variants identified were in the following genes: *MUTYH, BRCA2, LZTR1, MBD4* each with 2 carriers and singletons in the following genes: *MITF, MSH3, MSH6, RAD51C, RET, SDHD*, and *TSC1*. Notably, several of these genes (such as *RET, SDHD*, and *TSC1*) are implicated in syndromes associated with increased NET risk.

CONCLUSIONS

A considerable subset (15%) of HNP participants with NETs were found to have germline pathogenic variants, including alterations in genes relevant to NET predisposition. These findings highlight the potential value of population level genomic screening for identifying individuals at elevated risk for NETs and defining specific germline risks for various NET phenotypes. Expanding these findings across broader genomic screening programs has potential to demonstrate the importance of integrating germline testing into NET risk assessment and management strategies. Further studies are warranted to determine the clinical significance of these and more variants in NET development, progression, and outcomes.

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